REMARKS

Claims 1-3, 5-11, 13-21 and 25 are pending. Claims 1, 2, 5-8, 14 and 18-21 have been amended. Reconsideration of the present application is respectfully requested in view of these amendments and the comments that follow.

Claims 1-3, 5-11, 13-21 and 25 are definite and particular

The Office has rejected claims 1-3, 5-11, 13-21 and 25 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Although Applicants disagree with the Office regarding this rejection, the relevant pending claims have been amended to recite sequence identity with the amino acid residues provided in new SEQ ID NO: 3. The new sequence provided represents the mature for of VEGF. These amendments were made solely to clarify the subject matter of the invention at the request of the Examiner.

Claims 1-3, 5-11, 13-21 and 25 are unobvious over the cited art

The Office has rejected claims 1-3, 5-11, 13-21 and 25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tischer *et al.* (U.S. Patent No. 5,194,596), in view of Claffey *et al.* (BBA 1246:19 (1995)), Yamaguchi *et al.* (U.S. Patent No. 5,648,233) and Thim *et al.* (U.S. Patent No. 5,783,416). To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art must reference must teach or suggest all the claim limitations. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The pending claims recite a vascular endothelial growth factor (VEGF) dimer, where each monomer has a particular amino acid sequence and that each cysteine (Cys) residue at or corresponding to position 116 of each monomer is disulfide-bonded to an additional extraneous Cys, and where at least one of the monomer lacks a glycosylation site at or corresponding to positions 75-77 of a mature VEGF monomer because of an Asn to Glu mutation.

The Office alleges that Tischer *et al.* teach the claimed VEGF protein, which, when refolded in the presence of glutathione inherently has an extraneous Cys residue disulfide-bonded to the Cys

residue corresponding to position 116 of the claimed protein. Additionally, the Office alleges that it would have been obvious to one of ordinary skill in the art to mutate the VEGF sequence of Tischer *et al* to destroy the glycosylation site over the teachings of Claffey *et al.*, in view of Yamaguchi *et al.*, and/or Thim *et al.* Applicants respectfully disagree.

Tischer *et al.* does not inherently teach disulfide-bonding extraneous Cys residues to a Cys residue at or corresponding to Cys-116

The Office alleges that the pending claims are *prima facie* obvious over Tischer *et al.*, which teaches a recombinant VEGF protein of 121 amino acids in length that is refolded after bacterial expression using glutathione. The Office alleges that it would be expected that proteins having glutathione bound to Cys-116 would result from the techniques taught by Tischer *et al.* Tischer *et al.* does not explicitly teach a recombinant VEGF protein having glutathione at or corresponding to Cys-116 of each and every monomer, as recited in the pending claims. Instead, the Office relies upon a "finding of inherency" to support the prima facie case of obviousness based on Tischer *et al.* (Office Action, page 4.)

In attempting to use the doctrine of inherency to establish that Tischer *et al.* inherently taught or suggested a feature of the pending claims, the Office must overcome two hurdles. The first hurdle requires the Office to demonstrate that the allegedly inherent feature necessarily flows from the teachings of the reference. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency.]" *In re Oelrich*, 666 F.2d 578, 581-582 (CCPA 1981). The second hurdle requires that the Office demonstrate that the allegedly inherent feature would have been recognized by one of ordinary skill in the art as being present in the reference before the invention of the claimed invention. "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d 44, 448 (CCPA 1966). Because the Office has failed to demonstrate that the teachings of Tischer *et al.* necessarily meet the limitation of claim and that a skilled artisan would have recognized the presence of the allegedly inherent feature, the Office has failed to clear either of these hurdles.

The Office alleged that Tischer *et al.* inherently teaches a recombinant VEGF protein having an extraneous Cys disulfide-bonded to a residue at or corresponding to position 116. The teachings of Tischer *et al.* may very well provide a method by which some Cys residues at or corresponding to position 116 of a mature recombinant VEGF sometimes are disulfide-bonded to an additional extraneous Cys, such as the one found in glutathione. What the Office has not shown, however, is that the teachings of Tischer *et al.* always and necessarily provide for a Cys residue at or corresponding to position 116 of a mature recombinant VEGF that is disulfide-bonded to an additional extraneous Cys. Because the Office has not demonstrated or even alleged that the teachings of Tischer *et al.* necessarily teach or suggest modifying a recombinant VEGF protein such that it has an extraneous Cys residue disulfide bonded to a VEGF residue at or corresponding to Cys 116 of the mature protein, Tischer *et al.* cannot be said to support a *prima facie* case of obviousness.

Even reading Tischer *et al.* in a favorable light, the Office has failed to demonstrate that one of ordinary skill in the art would have recognized that the teachings of the reference would lead a skilled artisan to consider production of the claimed recombinant protein obvious. The Office provides absolutely no support for the allegation that one of ordinary skill in the art would have considered making the presently claimed invention. At best, the Office, using impermissible hindsight, points to Tischer *et al.* to find a claim limitation that was allegedly inherent in the reference. Inherency, however, is not a substitute for some teaching or suggestion to support the present obviousness rejection. *See In re Rijckaert*, 9 F.3d 1531, 1534 (CAFC 1993) *citing In re Newell*, 891 F.2d 899, 901 (CAFC 1989). The Office has failed to identify any teaching or suggestion in Tischer *et al.* to support the *prima facie* case of obviousness leveled against the pending claims. As such, the Office has failed to articulate a prima facie case of obviousness based on Tischer *et al.*, whether taken alone or in combination with the prior art cited.

Amino acid substitution

The pending claims recite recombinant VEGF monomers formed into a dimer where at least one of the monomers lacks a glycosylation site because of an Asn to Glu amino acid substitute at the glycosylation site found at residues 75-77 of the mature protein. Tischer *et al.* does not teach or

suggest this specific mutation. At best, Tischer *et al.* teaches that glycosylation is not necessary for VEGF activity.

To overcome this shortcoming of Tischer *et al.*, the Office cites Claffey *et al.*, who teach an Asn to Tyr amino acid substitution. The Office then resorts to Yamaguchi *et al.* and Thim *et al.* who teach conservative amino acid substitutions in proteins other than VEGF. The Office concludes that it would have been obvious to a skilled artisan to modify the protein of Tishcer *et al.* by substituting the native Asn with a Tyr residue, as taught by Claffey *et al.* even though Claffey *et al.* disparaged this mutation. According to the Office, the skilled artisan would then have recognized that the non-conservative substitution taught by Claffey *et al.* could be replaced by a conservative substitute of Asn to Glu, as taught by Yamaguchi *et al.*, and/or Thim *et al.* Applicants respectfully disagree with the reasoning of the Office.

The elaborate combination of references cited by the Office fails to provide the requisite motivation to modify Tischer *et al.* to achieve the claimed invention. The Office has provided a series of disjointed points in an attempt to render the claimed modification of the amino acid sequence of VEGF was obvious. What the Office has failed to provide, however, is any modicum of support for one of ordinary skill in the art to connect those points to achieve the claimed invention.

Let us look at the various points. After Tischer *et al.*, which teaches VEGF variants, the Office cites Claffey *et al.*, which teaches an Asn to Tyr mutant that destroys the N-linked glycosylation site. Claffey *et al.* note that this mutant "produced an inefficiently secreted dimeric protein" (Claffey *et al.*, Abstract). According to the Office, the skilled artisan would not be daunted by this set back. Instead, according to the Office, the artisan would look to the teachings of Yamaguchi *et al.* or Thim *et al.* to solve this problem. Why? Because the mutation suggested in Claffey *et al.* didn't work so, according to the Office, this failure would motivate a skilled artisan to look to work on unrelated proteins for the teachings necessary to achieve the claimed invention.

Yamaguchi *et al.* teach a modified tumor cytotoxic factor with a mutation that eliminates the glycosylation site in the protein. Yamaguchi *et al.* teaches that Gln is the preferred substituting amino acid residue, with Asp, Glu, His, Ser or Thr being acceptable (Yamaguchi *et al.*, col. 2, lines 41-43). Thim *et al.* teach a mutation in human spasmolytic polypeptide Asn to Glu (Thim *et al.*,

col. 4, lines 49-54). Neither Yamaguchi *et al.* nor Thim *et al.* teach or suggest modifying the glycosylation site within VEGF. In fact, these references don't even mention VEGF. These references also do not cure the deficiencies in Claffey *et al.*

The motivation to modify Claffey *et al.* to achieve the claimed invention cited by the Office is based on the failure of this reference to express the recombinant protein properly. Rather than providing a motivation to modify the cited references, Claffey *et al.* actually teaches away from modifying VEGF to destroy the glycosylation cite, given the reduction in protein production. Because the Office has failed to articulate a *prima facie* case of obviousness, Applicants respectfully request that the present rejection of the claims be withdrawn.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 219002031120. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 27, 2004

Respectfully submitted,

By _____

James J. Mullen, III, Ph.D.
Registration No.: 44,957
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130
(858) 720-7940